C1 SUB D2

20. (Amended) An isolated, purified or recombinant polynucleotide encoding a mouse telomerase reverse transcriptase (mTERT) protein, wherein said protein:

(i) has at least 90% sequence identity to SEQ ID NO:2; and,

(ii) has telomerase catalytic activity when associated with a telomerase RNA.

C2 SUB D3

28. (Amended) A mouse cell in which an endogenous mTERT gene in the cell has been mutated by recombinant means, [wherein said cell is deficient in telomerase catalytic activity,] or progeny of said cell.

REMARKS

I. Status

After entry of this Amendment, Claims 20-28 are pending in the present application. Claims 20 and 28 have been amended. All claims stand rejected.

II. Amendments

Claim 20 has been amended to more clearly state the claimed invention. Claim 20 now specifically recites that the encoded mTERT polypeptide possesses telomerase catalytic activity when associated with a telomerase RNA component (e.g., mTERC or hTERC). Support for this amendment is found in the specification at, e.g., page 68, lines 15-21, and 118, lines 1-11 and page 91, lines 5-10.

The cancellation or amendment of claims by Applicants is made without prejudice to future prosecution of the original claims, and should not be interpreted as agreement with the rationale for rejection articulated by the Office.

III. The Claims

Claim 20 is directed to polynucleotides encoding the naturally occurring mouse TERT protein sequence set forth as SEQ ID NO:2 or variants with at least 90% sequence identity to SEQ ID NO:2. The encoded protein variants of Claim 20, as amended, must possess telomerase catalytic activity when associated with a telomerase RNA. Claim 21 is directed to those polynucleotides which encode a mTERT protein of the specific sequence set

forth in SEQ ID NO:2. Claim 22 is directed to a polynucleotide with the sequence of SEQ ID NO:1. Claims 23-25 are directed to cells comprising a polynucleotide of Claim 20, 21, or 22. Claims 26-27 are directed to expression vectors comprising these polynucleotides.

Claim 28 is directed to a mouse cell in which an endogenous mTERT gene in the cell has been mutated by recombinant means.

IV. Rejections Under 35 U.S.C. §112, First Paragraph

A. Written Description

Claims 20-27 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention. Regarding this rejection, the Office Action asserts the following:

> There is no description of mutational sites that exist in nature and there is no description of how the structure of mTERT relates to the structure of different alleles. In addition, according to the standard definition of allelic variants [sic] the genus include members that would be expected to have widely divergent functional properties....The specification as filed fails to identify the common attributes of individual alleles other than SEQ ID NO:1 and 2. According to these facts, one skill [sic] in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Thus, the Office Action's argument for this rejection appears to be that the written description found in Applicants' specification is allegedly not commensurate with the scope of Claims 20-27.

This rejection is respectfully traversed.

Under *Vas-Gath, Inc. v. Marhurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), an applicant's invention must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention". As outlined in the "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1, 'Written Description' Requirement'" (*Federal Register*, December 21, 1999, 64:71427-71440), the written description requirement for a claim drawn to a genus may be satisfied by "disclosure of relevant identifying characteristics, i.e., structure

or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics" (page 71436). The "Revised Interim Guidelines" indicates that a disclosure of even partial structural properties may be sufficient (page 71436). Although a representative number of species must be sufficiently described for a generic claim, the variety of described species that is required need only parallel the variation which exists within the genus (see the definition of "representative number of species" on page 71436 of the "Revised Interim Guidelines").

Applicants submit that their specification provides sufficient written description to support the generic claims of Claims 20, 23, and 26. In contrast to the statements made in the Office Action, Applicants' specification as originally filed *does* disclose common attributes for the members of the claimed genus. These common attributes consist of the combination of a functional characteristic with structural information, thereby defining identifying characteristics of members of the genus in complete accordance with the above-cited "Revised Interim Guidelines". The phrase "has at least 90% sequence identity to SEQ ID NO:2" of the independent claim, Claim 20, provides substantial structural information about the members of the genus. An example of a polynucleotide sequence which encodes the mTERT protein sequence of SEQ ID NO:2 is provided in SEQ ID NO:1. In addition to the structural information, Claim 20 recites a description of a required functional characteristic for each member of the claimed genus by reciting that each of the encoded proteins must have "telomerase catalytic activity". Support for this functional characteristic is replete in the specification (see, e.g., pages 63-68, page 118, lines 1-11).

Not only do Applicants teach both functional and structural characteristics, in addition the specification discloses correlation between the structural information and the functional activity. For instance, the specification teaches substantial information about conserved motifs within the TERT protein sequence. See, for instance, Figures 4 and 5 page 21, line 6, to page 24, line 3. Based on Applicants' disclosure, one of ordinary skill in the art would have understood that disruption of amino acid residues within the conserved motifs could disrupt telomerase catalytic activity. One of ordinary skill in the art would have readily understood, in contrast, mutation of residues that show little or no conservation across species

would be unlikely to abolish telomerase catalytic activity. Thus, the specification clearly conveys that Applicants were in possession of the claimed invention.

Furthermore, although the Office Action asserts that the members of the genus would be expected to have widely divergent properties, this assertion ignores that fact that the members of the genus are defined in part by the common property of having telomerase catalytic activity. Thus, at least with regard to this key functionality, the variants of Claim 20 cannot be widely divergent, or even divergent. Furthermore, structural variations among members of the claimed species will also not be great, since all members of the genus of Claim 20 must encode proteins with at least 90% homology to SEQ ID NO:2. Because there is minimal structural and functional variation between the members of the presently claimed genus, by teaching the sequence of SEQ ID NO:2 and SEQ ID NO:1, along with the conserved motif teachings referred to above, Applicants have sufficiently described a representative numbers of species of Claim 20.

Claims 21-22, 24-25, and 27 Recite Specific Sequences Supported in the Specification

Applicants further submit that the specification clearly describes the subject matter of Claims 21-22, 24-25, and 27. As detailed above, the arguments presented by the Office Action are directed only to those claims which are generic claims encompassing polynucleotides encoding mTERT variants. Claims 21 and 22, however, are not directed to polynucleotides which encode mTERT variants. Instead, **these claims are directed to polynucleotides that encode the defined sequence corresponding to SEQ ID NO:2 or that themselves comprise the defined sequence corresponding to SEQ ID NO:1**. All of the arguments in the Office Action regarding sufficient written description for the mTERT variants are therefore irrelevant to Claims 21 and 22. In addition, Claims 24-25 and 27 are dependent upon Claims 21 and 22. Therefore, arguments presented in the Office Action are also completely irrelevant to these claims. Because the sequences of SEQ ID NO:1 and SEQ ID NO:2 and their uses in cells and expression vectors were disclosed in the Application as originally filed, one of ordinary skill in the art would have undeniably recognized that Applicants were in possession of the invention of Claims 21-22, 24-25 and 27.

In light of the foregoing remarks, Applicants respectfully request that the rejection of Claims 20-27 under 35 U.S.C. §112, paragraph 1, as allegedly not being described by the specification, be withdrawn.

B. Enablement

1. Claims 20-27

Claims 20-27 were also rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Office Action states the following:

> The specification as filed fails to disclose all polynucleotide sequences that has [sic] 90% sequence identity to SEQ ID NO:2 and has telomerase like activity....Furthermore, it is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted. For example, mutation of key residues in TERT gene are know [sic] to abolish the telomerase activity (Lundblad, PNAS, 95:8415-8416, 1998, page 8415, col.1 para.2, page 8416 col.1, para 2-3). Consequently, excessive trial and error experimentation would be required to identify the necessary nucleic acid sequence derivatives encoding a biologically active polypeptide with an amino acid sequence differing from SEQ ID NO:2, since the amino acid sequence of such polypeptide could not be predicted *a priori.*

This rejection is respectfully traversed.

Enablement under §112, first paragraph, requires "that the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A requirement for some experimentation, such as routine screening, does not indicate a lack enablement. Enablement simply requires that the necessary experimentation not be undue. *In re Wands*, 858 F.2d at 736-737. *See also* MPEP 2164.01.

Applicants submit that their specification as originally filed fully enables Claims 20, 23, and 26 under the standard articulated in *In re Wands*. Applicants respectfully disagree with the assertion by the Office Action that one of ordinary skill in the art would not be able to make and use polynucleotides which encode active mTERT protein and mTERT protein variants without "excessive trial and error experimentation".

Polynucleotides encoding the mTERT protein variants can be readily prepared as taught by Applicants' specification when combined with the knowledge of one of ordinary skill in the art. Methods for isolating, identifying, synthesizing, purifying, and amplifying polynucleotides which encode mTERT protein or its variants are described at, e.g., pages 20 to 35 and on pages 94 to 101 of Applicants' specification. Guidance on expression of the polynucleotides is found at, e.g., pages 36 to 46 and at pages 103 to 111 of the specification. Purification methods suitable for use with the encoded mTERT variants can be found at, e.g., pages 51 to 63 of the specification. Reconstitution of mTERT telomerase activity is taught at, e.g., page 118, lines 1-21.

Applicants further submit that the polynucleotides of Claims 20, 23, and 26 could have been obtained by one of ordinary skill in the art without the "excessive trial and error experimentation" asserted in the Office Action. The Office Action points to the presence of "key residues" within the TERT protein sequence which most likely could not be altered without destroying telomerase activity. Applicants agree that such key residues exist within the mTERT sequence. Applicants' own specification teaches the presence and nature of conserved TERT protein motifs (e.g., Figure 4; Figure 5; line 6, page 21 to line 3, page 24). The Office Action, however, is mistaken in its suggestion that the availability of such knowledge to one of ordinary skill in the art at the time of the filing would have hindered the ability of the artisan to make and use the claimed invention. Quite to the contrary, the identification of conserved residues would have contributed to the skilled artisan's ability to predict which amino acids residues likely could be mutated without a loss of catalytic activity. Polynucleotides that encoded mTERT proteins with mutations in the conserved motifs would generally have been avoided by one of ordinary skill in the art. In addition, even without the helpful guidance of the conserved motifs provided by present Applicants, the majority of variants of mTERT with 10% or less mutation compared to SEQ ID NO:2 would be expected to retain telomerase catalytic activity. Thus, undue experimentation would not have been required by one of ordinary skill in the art to obtain active variants of mTERT with greater than 90% homology to SEQ ID NO:2.

Furthermore, even absent the guidance of the specification identifying conserved motifs, the polynucleotides of Claim 20 could still have been readily prepared

without undue experimentation. A particular polynucleotide encoding a mutant mTERT with at least 90% homology with SEQ ID NO:2 could first have been made or isolated as outlined above and then the encoded protein would simply have been assayed for catalytic activity. Although screening for catalytic activity would entail some experimentation, the experimentation would have been routine given the teachings provided by Applicants' specification and the knowledge of those of ordinary skill in the art. For example, a number of different techniques for assaying the catalytic activity of mTERT proteins can be found at page 63, line 21, through page 67, line 27 of Applicants' specification. For instance, the TRAP assay is well known as an assay for telomerase enzymatic activity and is described at page 66, line 19, to page 67, line 19, of the specification. The assay is not particularly technically difficult and is highly sensitive. Once a given mTERT variant is made, it would have been well within routine experimentation for one of ordinary skill in the art to have assayed the protein for reverse transcriptase activity. As dictated by *In re Wands*, a requirement for routine screening does not indicate a lack of enablement. *In re Wands,* 858 F.2d at 736-737.

Although the Office Action asserts that excessive trial and error would be required to make and use the invention because the amino acid sequence of the encoded mTERT variants allegedly "could not be predicted *a priori*" (Office Action at page 4), *a priori* prediction is not the legal standard for a rejection under § 112. As already articulated above, the test for enablement is whether undue experimentation is required, not whether *a priori* prediction of every embodiment of an invention is likely. *See* MPEP 2164.01. "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands,* 858 F.2d at 736-737. Applicants therefore submit that the sequence of the mTERT polypeptide variants do not need to be predictable *a priori* for the present claims to be enabled.

The Office Action also makes repeated reference to the "telomerase complex" in its arguments, asserting that the "telomerase complex" consists of multiple components in addition to TERT, such as an RNA component and some associated proteins. However, while the other components of the telomerase complex may play roles in telomerase activity, any discussion of the other components of the telomerase complex is irrelevant to the patentability of the present claims which are directed solely to polynucleotides encoding mTERT polypeptides.

The specification also provides sufficient enablement of Claims 21-22, 24-25, and 27. As was the case with the written description rejection (see above), the arguments for the lack of enablement rejection presented by the Office Action appear to be directed only to those claims which are generic claims encompassing polynucleotides encoding mTERT variants. **As previously discussed, such arguments are completely irrelevant to Claims 21, 22, 24-25, and 27, which relate to polynucleotides that encode mTERT proteins of SEQ ID NO:2**, not mTERT variants. All of the arguments in the Office Action regarding lack of enablement for the mTERT variants are therefore irrelevant to Claims 21-22, 24-25, and 27. Further, working examples of the polynucleotides of Claims 21 and 22 are provided in Example 1, line 26 of page 96 to line 20 of page 99 of Applicants' specification. The production of cells and expression vectors comprising the polynucleotides (claims 24-25, and 27) are clearly enabled by the combination of Applicants' specification with the conventional methods of the art. Thus, Claims 21-22, 24-25, and 27 are fully enabled.

In light of the foregoing remarks, Applicants respectfully request that the rejection of Claims 20-27 under 35 U.S.C. §112, paragraph 1, as allegedly not being enabled by the specification, be withdrawn.

2. Claim 28

Claim 28 was also rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In articulating the rejection, the Office action states the following:

> ...the specification as filed fails to disclose a mouse cell in which endogenous mTERT gene has been mutated by any recombinant means and the cell is deficient in telomeres [sic] activity....the phenotype of targeted mutations by a homologous recombination have not always been as predicted from the knowledge of the nature of the gene product and its pattern of expression (Rossant et al , Phil. Trans. R. Soc. Lond. B. 339:137-254, 1993; page 71 col.2 par.2). Thus, in view of unpredictable nature of homologous recombination and lack of specific guidance in the specification, the skilled artisan at the time of filing would be unable to use the claimed invention.

Applicants respectfully traverse.

Applicants submit that their specification fully enables the "knock-out" mouse cell of Claim 28. The previous Office Action, mailed October 13, 1999, correctly acknowledged that, provided with the disclosure by the instant inventors of mTERT gene sequence, the "mTERT gene can be 'knocked out' using conventional techniques usually involving homologous recombination" (page 7, second paragraph, of the 10/13/99 Office Action; emphasis added). Applicants further note that the subject matter of Claim 28 is taught in the following sections of the specification: line 3 of page 47 to line 22 of page 49; lines 13-30 of page 71; Example 4 of pages 111-116; and Figure 9. Applicants' specification thus provides an abundance of step-by-step instruction on how to disrupt an mTERT gene in a mouse cell. Applicants believe it is beyond dispute that Claim 28, as now amended, meets the standard for enablement.

Furthermore, contrary to the assertion of the Office Action, the phenotype of an mTERT "knock-out" mouse cell taught by Applicants is not unpredictable. First, the Office Action greatly overestimates the likelihood that "knocking out" a gene would fail to disrupt the immediate gene function. To support its assertion that the phenotypes of targeted mutations have not always been as predicted, the Office Action cites Rossant *et al.*. Rossant *et al.* does indicate that in a couple of *extreme* cases no *obvious* change in phenotype was observed when a gene was disrupted, such as when the p53 and *PrP* genes were disrupted in mice (page 71, column 2, second paragraph). However, the same reference also acknowledges that the predicted and actual outcome of disrupting is very close for certain genes (page 71, column 2, second paragraph). The Office Action has provided no evidence or argument to support its assertion that the disruption of the mTERT gene in particular would be one of the rare "extreme" cases alluded to by Rossant *et al.* where gene disruption would not produce the predicted outcome. Thus, the Office Action has failed to meet its burden of establishing a *prima facie* case for lack of enablement.

Second, Applicants submit that the p53 and PrP knock-out experiments cited by Rossant *et al.* provide no information on the predictability that disrupting the *mTERT* gene would cause a deficiency in telomerase catalytic activity. Any unpredictability of the phenotype of the p53 knockout mouse appears to have come from a lack of understanding of the complex nature of the gene function of the tumor suppressor gene p53. Although p53-

deficient mice appeared developmentally normal, they did exhibit a marked, and rather predictable, phenotype — an abnormal susceptibility to spontaneous tumors (see Rossant *et al.*, page 71, column 2, and abstracts of Donehower *et al.*, *Nature* 356:215-21, 1992, Harvey *et al.*, *FASEB J.*, 7:938-43, 1993, and Selkirk *et al.*, *Appl. Theor. Electrophor.*, 4:89-93, 1994). Similarly, although PrP-null mice apparently showed normal development and behavior, not surprisingly, the mice lacking prion protein were found to be highly resistant to prion diseases (see abstracts of Weissmann *et al.*, *Ann. NY Acad. Sci.*, 724:235-40, 1994, Raeber *et al.*, *Brain Pathol.* 8:715-33, 1998, and Sailer *et al.*, *Cell*, 77:967-8, 1994). If the normal development or behavior of the mice following *PrP* knock-out caused any surprise, it was because the full function of the PrP protein was not fully or exactly understood, not because disruption of the *PrP* gene failed. Any such lack of understanding about the nature of p53 and PrP has no bearing on whether or not knocking out a gene encoding a known telomerase catalytic subunit will decrease telomerase catalytic activity in the cell. Thus, the Office Action has not provided any evidence or argument that the disruption of the mTERT gene as taught by the present Applicants would not have produced a mouse cell deficient in telomerase catalytic activity as expected.

In fact, it would have been wholly predictable that disruption of the gene encoding mouse telomerase reverse transcriptase (mTERT) would have resulted in a loss of telomerase catalytic activity, since it had been shown that TERT contains the catalytic moiety of telomerase (see Applicants' specification, page 2, line 2, through page 3, line 5). Also, the ability to disrupt telomerase activity, by disrupting a gene encoding another component of the telomerase complex, the telomerase RNA component, had been previously shown by Blasco *et al.*, *Cell*, 91:25-34, 1997 (see page 115, line 17, to page 116, line 16, of Applicants' specification). Furthermore, since the filing of the present Application, an article has been published which reports the successful production of mTERT knock-out mice (Nikaido *et al.*, *Genes Cells* 4:563-572, 1999; copy enclosed). Nikaido *et al.* report that tissue cells derived from the mTERT knock-out mice lacked telomerase activity (see abstract), thereby clearly indicating that disruption of the mTERT gene in a cell does lead to a deficiency in telomerase activity in the cell. Applicants, therefore, assert that one of ordinary skill in the art would have

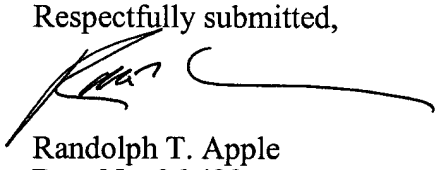
been able to make and use the mouse cell of Claim 28 based on the teachings of Applicants' specification and the ordinary knowledge of the art.

In light of the foregoing remarks, Applicants respectfully request that the rejection of Claim 28 be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 650-326-2400.

Respectfully submitted,



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